Second-Line Therapies in Metastatic Urothelial Carcinoma

Sujata Narayanan, MD[a], Lauren C. Harshman, MD[b], Sandy Srinivas, MD[a,*]

KEYWORDS

• Refractory • Therapies in urothelial cancer • Chemotherapy • Targeted • Immunotherapy

KEY POINTS

- There is no standard of care treatment that improves patient survival.
- Taxanes in the US and Vinflunine in Europe are the most commonly used agents.
- Participation in clinical trials is critical.

INTRODUCTION

Platinum-based chemotherapy regimens have shown significant clinical activity against urothelial carcinomas (UC) and are generally used in the first-line setting. These regimens include combinations such as gemcitabine and cisplatin (GC) and methotrexate, vinblastine adriamycin, cisplatin (MVAC). Although these regimens have initial high response rates (RRs), ranging from 40% to 70%, they are generally not curative, with median progression-free survival (PFS) of approximately 8 months and a 5-year overall survival (OS) of 15%.[1,2] Most of these patients relapse and require additional therapy, but often, in the setting of decreased performance status and impaired renal function, precluding further administration of cisplatin.

Once patients progress or relapse after initial platinum-based chemotherapy, there is no standard of care treatment in the United States, despite scores of trials attempting to identify agents that improve patient survival. Further complicating matters, these patients tend to be older (median age, 70s), with multiple comorbidities. Selection of second-line or salvage treatment requires careful consideration of their prognosis, performance status, and organ function.

[a] Department of Medicine, Stanford University School of Medicine, Blake Wilbur Drive, Stanford, CA 94305, USA; [b] Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Harvard Medical School, 450 Brookline Ave, DANA 1230, Boston, MA 02215, USA
* Corresponding author.
E-mail address: sandysri@stanford.edu

Hematol Oncol Clin N Am 29 (2015) 341–359
http://dx.doi.org/10.1016/j.hoc.2014.10.007 **hemonc.theclinics.com**
0889-8588/15/$ – see front matter

CLINICAL PROGNOSTIC FACTORS

Various clinical prognostic factors have been identified in patients with advanced UC. In a retrospective analysis of patients treated with first-line MVAC,[3] Karnofsky Performance Score less than 80% and presence of visceral (lung, liver, or bone) were found to be 2 independent risk factors in predicting survival. When classified by the number of risk factors, 3 groups clearly emerged, with differential survival estimates. Patients with zero, 1, or 2 risk factors were found to have a median OS of 33, 13.4, and 9.3 months, respectively.

In the platinum-refractory second-line setting, performance status and liver metastasis continue to portend worse survival. In addition to these factors, Bellmunt and colleagues[4] identified anemia, defined as a hemoglobin level less than 10 g/dL, as an additional prognostic factor in patients with platinum-refractory UC who were treated with vinflunine. Based on the presence of zero, 1, 2, or 3 prognostic factors; the median OS was 14.2, 7.3, 3.8, and 1.7 months (P<.001), respectively. In a retrospective review of 7 prospective second-line phase 2 trials, shorter time from previous cisplatin therapy to start of subsequent therapy also portended worse survival.[5] In the randomized phase 3 trial comparing vinflunine in combination with best supportive care (BSC) with BSC in patients relapsing after first-line platinum-based chemotherapy, patients who had received previous cisplatin had overall more favorable prognostic criteria (better performance status and absence of visceral metastasis or anemia) and improved OS.[6,7]

BIOLOGY OF ADVANCED UROTHELIAL CARCINOMA

Until recently, the biology of progression in UC after response to previous therapy was poorly understood. Accumulating molecular data have now provided an improved understanding of the underlying tumor biology, and multiple candidate genes have been implicated in the pathogenesis and resistance mechanisms of UC. In advanced UC, alterations in various signaling pathways have been observed, involving angiogenesis (VEGFR [vascular endothelial growth factor receptor], FGFR [fibroblast growth factor receptor], angiopoietin receptor 1 and 2), survival (PI3K/AKT/mTOR [phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin] pathway, phosphatase and tensin homolog [PTEN], tumor protein p53), and proliferation (MAPK/ERK [mitogen activated protein kinase/extracellular signal-regulated kinases], EGFR [epithelial growth factor receptor], HER2 [human epidermal growth factor receptor 2], JAK-STAT [Janus kinase and signal transducer and activator of transcription]), have been observed, and are frequently associated with poor outcomes.[8–11]

Recently, a comprehensive profiling of muscle-invasive UCs by The Cancer Genome Atlas (TCGA) project showed 29 recurrently mutated genes, and several potential therapeutic targets in UC, including alterations in PIK3CA, HER2, FGFR3, TSC1 and HER3, as well as mutations in chromatin-regulating genes MLL, MLL2, MLL3, CREBBP, CHD7, SRCAP, ARID1A, KDM6A (UTX), and EP300.[12] Several of the genomic alterations identified in this study, particularly those involving the PI(3) K/AKT/mTOR, , MAPK, HER2, HER3, FGFR3 and CCND1 (cyclin D1) are amenable in principle to therapeutic targeting.

Encouraging preclinical and clinical data have recently emerged in tumor immunology with therapies focused on enhancing T-cell responses against cancer.[13–15] PD-L1 (programmed death ligand 1) is an extracellular protein that downregulates immune responses primarily in peripheral tissues by binding to its receptor, PD-1 (pro- grammed death 1). The interaction of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells.[16]